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GRANT NO: DAMD17-94-J-4276

TITLE: "Lymphedema:" Incidence, Time Course and Etiology in Long-term Survivors of Breast Cancer Cohort

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REPORT DATE: September 1995

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	September 1995	Annual (1 Sep 94 - 31 Aug 95)

4. TITLE AND SUBTITLE
"Lymphedema:" Incidence, Time Course and Etiology in Long-term Survivors of Breast Cancer Cohort

5. FUNDING NUMBERS
DAMD17-94-J-4276

6. AUTHOR(S)
Jeanne A. Petrek, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Sloan-Kettering Institute for Cancer Research
New York, New York 10021

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

We are employing an existing extensive data base on a cohort of patients treated consecutively between October 1976 and June 1978 who were known to be free of recurrent breast cancer 10 years after diagnosis. The existing data base includes prospectively acquired information (regarding clinical characteristics, intraoperative factors, pathological factors) and the annually-updated medical and cancer history. The medical records have been reviewed for specific anatomical and surgical technique factors that were not part of the original data base but may be associated with lymphedema development. We are interviewing each survivor for a wide range of factors occurring since her cancer treatment, concerning upper extremity activity, function, injury, infection, as well as general activity and health status. We are collecting subjective measurements of lymphedema as well as objective self-reported measurements of arm circumferences. With this study design, we will calculate incidence and rate of lymphedema development. In a nested case-control analysis the women with lymphedema will be matched with women of the same age and stage without lymphedema in order to identify differences that may be predictive of lymphedema development.

14. SUBJECT TERMS	15. NUMBER OF PAGES
breast cancer lymphedema, arm swelling	12
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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Jeanne Petrek 9/28/95

PI - Signature Date

Jeanne Petrek, MD

ANNUAL REPORT FOR GRANT NUMBER DAMD 17-94-J-4276

TABLE OF CONTENTS

Introduction

Nature of the Problem: Of all the permanent complications of breast cancer treatment, lymphedema is the most troublesome: The cosmetic deformity can not be disguised with normal clothing, physical discomfort and upper extremity disability is associated with the enlargement and recurrent episodes of cellulitis and lymphangitis may be expected in this setting. Added to the physical symptoms is the distress caused unintentionally by the clinicians, interested in cancer recurrence, who trivialize the non-lethal nature of lymphedema. At least 15% to 20% will develop lymphedema even after modern breast cancer treatment. It is estimated that 1-2 million breast cancer survivors are alive today and at least 200,000 of them cope daily with the disfigurement, discomfort and disability of arm and hand swelling. Despite the human cost, lymphedema has not been systematically studied.

Background of Previous Work: Dr. Jeanne A. Petrek, Principal Investigator, has completed and ongoing protocols involving short and long term complications after breast cancer treatment. (The only major long-term complication is lymphedema.) The research projects concern randomized exercise programs and intraoperative drain techniques. The patients in these research projects are being followed for lymphedema development. They comprise a group of over three hundred relatively recent patients with prospectively gathered clinical, pathologic, and other variables, including preoperative arm measurements by the research nurse. Meaningful data on lymphedema development will require several years. However, these patients are being followed with regular measurements of arm circumferences.

Purpose of the Present Work: We wish to document the incidence, time course, and predictive factors for lymphedema in the survivors of a breast cancer cohort. The current lack of knowledge of factors influencing lymphedema development mandates that all patients be instructed in the same arm and hand care precautions which may be too severe for those at low risk and yet not aggressive enough for those at the highest risk. The aim of the current project is to form a scale of risk for lymphedema depending on variables present at initial treatment and in the subsequent years. Prospective studies would then be performed to validate the scale of risk. As the longterm objective, future patients could receive more individualized anti-lymphedema precautions and a specific followup schedule for early detection of this complication depending upon their risk category.

Methods of Approach: The investigators possess a data base on 1,216 breast cancer patients treated consecutively between 1976 and 1978. It includes epidemiologic information gathered by interview at time of diagnosis, a detailed pathologic analysis, and initial/subsequent cancer and other illness treatment with followup status determined annually. Less than 2% have been lost at followup at 10 years. Study data will include subjective enlargement and arm circumference

measurements, as well as factors previously reported: age, obesity, extent of dissection, axillary radiation, and arm cellulitis/lymphangitis. The principal investigator's ongoing prospective studies have suggested: breast size, previous arm trauma/surgery, previous breast biopsy, number/proportion of positive lymph nodes, dominant hand on the treated side, specific surgical techniques and postoperative fluid formation. Factors in the subsequent years involving arm and general activity, infection and general health, etc. will be studied: occupations, sports, and hobbies, weight change, other illnesses, and arm/hand infections, injuries and surgeries.

Computer files from the existing database and the study data on arm/hand measurements and interview factors will be linked. Statistical analysis will include univariate and multivariate tests for the rate and a nested case control analysis for providing the odds ratio of lymphedema development related to various factors. Categories will be formed and risk of lymphedema will be rated according to pertinent variables present at time of diagnosis or in the ensuing years.

Body of Annual Report

Experimental Methods

1. As noted in the Introduction, at time of cancer treatment between 1976 and 1978, a large body of information was gathered and is available on the existing database. Nevertheless, it has required significant labor on the part of Ms. May Nah Ho, the statistician, and Dr. Ruby Senie, the epidemiologist, to rework the database into a form for this study. This included establishing an efficient format for the research nurse, Ms Margaret Peters, to utilize as the new study database enlarges. The prospectively gathered (in 1978-1978) variables are part of the lymphedema database: age, race, height/weight at diagnosis, obesity, menopausal status, previous medical history, medications, size of breast (weight of mastectomy specimen), dominant hand on the treated side, cancer primary size, histologic type/other characteristics, number/proportion of lymph nodes excised with metastatic cancer, perinodal spread.

2. Several variables present at time of operation in 1976 to 1978 were not collected at that time. These include various specific anatomical and surgical factors: excision of thoracodorsal nerve complex, excision of pectoralis minor muscle, length of operation, number of lymph nodes excised, highest level of lymph nodes excised, and specific on postoperative fluid formation, such as total volume of drainage and number of days with the drain. The charts of all study patients were requested, abstracted for these variables, and entered into the database. Since this part of the study data collection began, only 26 charts have not yet been accessed, usually due to their being sent to an outside location for microfilming.

3. The preparation of the telephone interview data collecting questionnaire required several revisions and each revision required further testing with non-protocol patients. The prototype form was utilized with great success in the principal investigator's smaller prospective study with 122 patients who had cancer treatment less than five years ago and who had been accrued preoperatively for the specific study of lymphedema. The interview instrument required the revisions mainly to account for the older age of patients in the present study.

Information obtained from interview consists of weight changes over the interval from diagnosis to the current time, illnesses, operations, medications, hospitalizations (to confirm the pre-existing database information of the annually updated medical history and cancer status), predominant occupation, hobby, sports in the years since diagnosis (for assessment of general and upper extremity activity level), and arm infection/injury or unrelated arm surgery with detailed data

on time of occurrence, length of hospitalization and disability.

4. The preparation of the form for self-reported arm circumferences required significant revisions and testing on non-protocol patients to allow for this specific population with their greater age, decreased dexterity, and sometimes slower comprehension of instructions.

Addressing tasks in the statement of work

In the Appendix page || please see the Statement of Work for the project "Lymphedema: Incidence, Time Course, and Etiologic Factors in Long Term Survivors of a Breast Cancer Cohort" that was included in the Army grant application.

Task 1 was achieved with multiple revisions for the appropriate data collecting instruments and returns to pilot testing on non-protocol patients.

Under task 2, the actual interviewing process and collection of self-reported measurements is proceeding. Although there was delay in beginning, with the process now efficient, this phase of the project should conclude on schedule. A full one-third of the study subjects have been contacted. Among these there has been excellent co-operation with the interview process. The self-reported measurements currently in progress have required more research nurse intervention with followup phone calls and reminders than predicted and this process has now been added to the operational system.

Ongoing data entry is proceeding on schedule, as listed in Task 2. c.

Report at Year 1, Task 2.d., is enclosed.

Conclusions

We are employing an existing extensive data base on a cohort of patients treated consecutively between October 1976 and June 1978 who were known to be free of recurrent breast cancer 10 years after diagnosis. The existing data base includes prospectively acquired information (regarding clinical characteristics, intraoperative factors, pathological factors) and the annually-updated medical and cancer history. The medical records have been reviewed for specific anatomical and surgical technique factors that were not part of the original data base but may be associated with lymphedema development. We are interviewing each survivor for a wide range of factors occurring since her cancer treatment, concerning upper extremity activity, function, injury, infection, as well as general activity and health status. We are collecting subjective measurements of lymphedema as well as objective self-reported measurements of arm circumferences with a method tested in non-protocol patients.

With this study design, we will have an accurate incidence and rate of lymphedema development of long-term survivors of a cohort of consecutively treated breast cancer patients. In a nested case-control analysis the women who developed lymphedema will be matched with women of the same age and stage who did not develop lymphedema in order to identify differences that may be predictive of lymphedema development. The odds of developing lymphedema according to the various factors will be calculated. A profile of the patient at low, middle, or high risk for lymphedema development will be constructed.

This analysis is urgent for the potential benefit of future breast cancer patients. Currently each woman is given instructions for arm/hand precautions without taking into account the individual risk factors pertaining to lymphedema development in that woman. However, a more biological approach would be individualization for the prevention precautions and a followup schedule for early detection of this complication based on the patient's risk. The high risk patient should be admonished in detailed precautions, with reminders at surgeon, radiotherapist, and medical oncologist visits and careful circumference or volumetric measurements at that time. The highest risk patients might fit into a pilot study for aggressive prevention and be fitted with a compression sleeve immediately after surgery. Conversely, patients at low risk would not be advised in the current set of instructions which ban vigorous exercise and even carrying one's purse on the treated side. The low risk would benefit since they could have greater normalcy in their life. Most patients, however, would probably be in the average risk category and still receive the same instructions in arm/hand precautions.

References none

APPENDIX

STATEMENT OF WORK

Lymphedema: Incidence, Time Course, and Etiologic Factors in Long Term Survivors of A Breast Cancer Cohort

Task 1. Months 1 -2

a. Final preparation of data collecting instruments.

b. Pilot study on non-protocol patients seen for routine followup.

Task 2. Months 3 - 14

a. Interview of study subjects

b. Collection of self-reported measurements

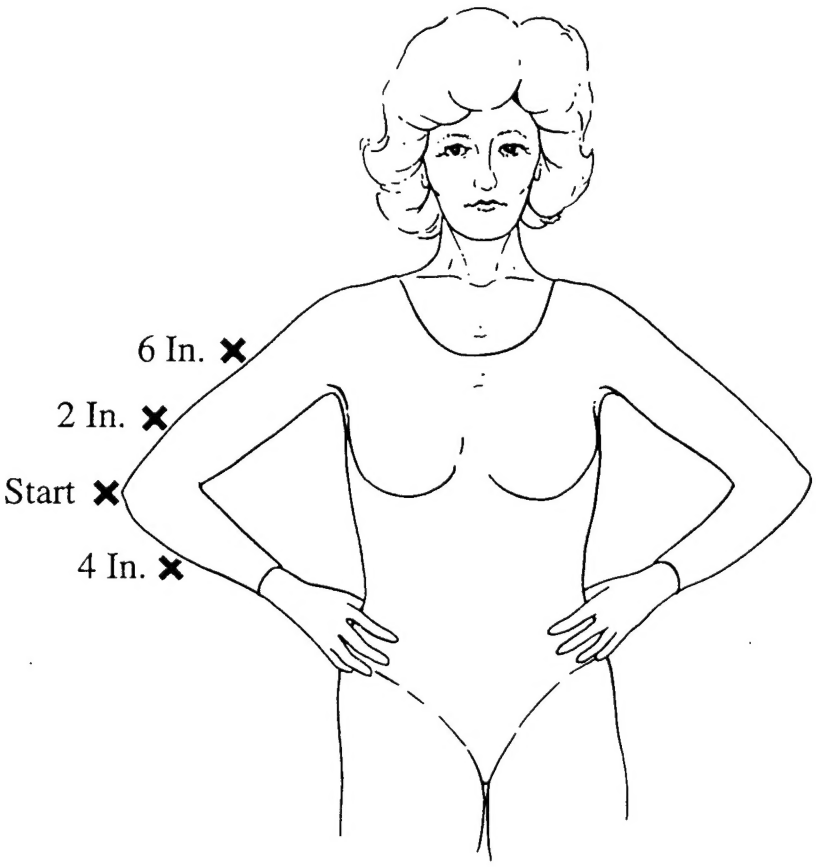
c. Ongoing data entry

d. Report at Year 1

Task 3:. Months 15 - 24

a. Data analysis

b. Manuscript/report



INSTRUCTIONS:

1. Please record measurements in inches (red arrow marks indicated on the enclosed tape).

2. Put the hand of the arm being measured on your hip (i.e. right hand on right hip). Please ask someone to assist you with the measuring of your arms.

	RIGHT ARM	LEFT ARM
3. Measure 2 inches above elbow (start at the pointy part of elbows)	_____	_____
Measure 6 inches above the elbow points	_____	_____
Measure 4 inches below elbow points	_____	_____